REMARKS

Claims 1 and 3-33 are pending. Claim 20 has been cancelled without prejudice or disclaimer and claim 1 has been amended. Support for the amendments to claim 1 is found *inter alia* in the claims and specification as originally filed. No new matter is added.

Rejections under 35 U.S.C. §§ 103(a)/101

Claim 20 was provisionally rejected as claiming the same invention as claim 20 of co-pending application USSN 10/574,302. Claim 20 was also rejected under 35 U.S.C. § 103(a) as unpatentable over Blondino (US 6,451,285) in view of Clarke (US2002/0103260). Without conceding the correctness of either rejection, and in order to advance the prosecution of the subject application, claim 20 has been cancelled by this amendment, rendering the rejections moot.

Rejections under 35 U.S.C. §§ 103(a)

Claims 1, 7, 10, 13-17, 21, 23, 24, 27, 28 and 32 remain rejected under 35 U.S.C. § 103(a) as unpatentable over Clarke (US 2002/0103260) alone; claims 3-6, 21, 22, 26, and 33 remain rejected over Clarke in view of U.S. Pub. No. 2003/0223939 ("Kordikowski"); and claims 8, 9, 11, 12, 18, 19, 25, and 29-31 remain rejected over Clarke in view of U.S. 6,475,467 ("Keller"). All three of these rejections are traversed.

Claim 1, as amended, is directed to a pharmaceutical aerosol suspension formulation for use in a metered dose inhaler (MDI) comprising formoterol fumarate dihydrate in suspension, a propellant and ethanol, wherein the formoterol fumarate dihydrate has a water content of 4.8 to 4.28% by weight, and a steroid in suspension. The remaining claims depend, directly or indirectly, from claim 1.

The problem addressed by the present invention is the need to provide a more stable aerosol suspension formulation of formoterol fumarate dihydrate (FFDH), which when formulated as suspended particles is prone to agglomeration, sedimentation, and adherence to the inner surfaces of both its storage canister and the valves of the inhaler device. *See e.g.*, the specification at p. 1, lines 10-29. A result of this formulation instability is irregular dosing. *Id.*

Applicant's solution to the problem of FFDH instability was to dry the FFDH "raw material" to a low water content before mixing with the other ingredients of the formulation. Specification at p. 3, lines 9-16; *see also* the specification at p. 6, lines 9-14 (stating that "by

subjecting the [FFDH] raw material to a drying step that is designed to drive off all, or substantially all, of the residual water but not the water of crystallization, formulations of very high stability can be achieved."). It was unexpectedly found that the "drier" formulations of the invention were more stable, as evidenced by their high Delivered dose Uniformity when discharged from an MDI device. *See e.g.*, the specification at p. 4, lines 4-9.

The superior stability of the "drier" FFDH formulations provided by the invention is evidenced by the data and supporting Declaration of Rudi Mueller-Walz under 37 C.F.R. § 1.132 which accompanies this response. The Declaration presents comparative stability data for a "dry" and a "wet" FFDH formulation following 12 months of storage. The two formulations are identical except for their water content. The formulation labeled "dry" has an FFDH water content of 4.42%. The formulation labeled "wet" has an FFDH water content of 5.11%. First, the data show that the dry formulation has superior dose uniformity. This is evidenced by the mean delivered dose which was shown to be much higher for the "dry" formulation compared to the "wet" formulation and also by the lower relative standard deviation (RSD) for the dry formulation. Second, the data show that the dry formulation retained a better fine particle fraction (FPF), which is the inhalable part of the delivered dose of the aerosol. This is evidenced by the higher fine particle dose obtained with the dry formulation as well as the lower RSD of the dry formulation.

The skilled person, relying on Clarke either alone or in combination with any of the other cited references, would have lacked any reason for making a FFDH aerosol suspension formulation having the FFDH water content specified in the claims. The only reason for ensuring that the FFDH has the specified water content is found in Applicant's specification, which teaches that this particularly low range of water content results in FFDH suspension formulations of high stability. None of the references teach or suggest this solution to the problem of increasing the stability of FFDH aerosol suspension formulations. Indeed, the combination of references is entirely silent with respect to the water content of the FFDH component. Further, a reasonable expectation of success is lacking where, as here, there is a complete lack of any guidance or direction in the combination of references that would point the skilled person toward making a drier FFDH according to Applicants' claims.

In summary, a *prima facie* case has not been established with respect to claim 1, or its dependent claims, because the cited reference fails to describe or suggest each and every element of the claimed invention. In particular, Clarke fails to describe or suggest a formulation comprising formoterol fumarate dihydrate in suspension, a propellant and ethanol, wherein the

formoterol fumarate dihydrate is provided as particles having a water content of 4.8 to 4.28% by weight. The remaining references do not overcome this deficiency of Clark. Accordingly, Applicant requests reconsideration and withdrawal of the rejection as applied to claim 1 and its dependent claims; as applied to claims 3-6, 21, 22, 26, and 33 (Clark in view of Kordikowski); and as applied to claims 11, 12, 18, 19, and 29-31 (Clark in view of Keller).

Response to Examiner's Remarks

In the Examiner's view, the fact that Clarke provides only one aerosol formulation while exemplifying 215 dry powder formulations is immaterial. Office action at p. 8. Applicant disagrees. This fact is material to both the reason and the reasonable expectation of success elements of the *prima facie* case. Clarke fails to provide either a reason or a reasonable expectation of success for making the claimed FFDH aerosol formulations, in view of the reference's limited teachings regarding aerosol formulations combined with its complete silence regarding the importance of FFDH water content in improving the stability of an FFDH aerosol suspension formulation. Absent Applicant's discovery that FFDH dried to low water content provided more stable aerosol suspension formulations of FFDH, the skilled person would have lacked any reason or expectation of success in making the claimed formulations.

The Examiner also stated that Applicant had not demonstrated the increased stability of the claimed formulations. It is noted that the Examiner's comment was directed to the stability of the dihydrate form over other forms of FF. Applicant has clarified in these remarks that the improved stability obtained by the claimed invention relates to the stability of the FFDH aerosol suspension formulation, as evidenced, *e.g.*, by the high Delivered dose Uniformity of an FFDH formulation having a water content within the claimed range as compared to one having a higher water content. The accompanying Declaration provides evidence to support the increased stability of the claimed "dry" aerosol suspension formulations of FFDH.

Double Patent Rejection

Claims 1, 3-19, and 21-33 are provisionally rejected on grounds of nonstatutory obviousness-type double patenting as unpatentable over claims 1, 3-19, and 21-33 of co-pending application USSN 10/574,302 in view of Clarke. The Examiner states that the only difference between the pending claims and the claims of the '302 application is that the steroid as claimed in the '302 application is in solution. The rejection is traversed.

While Clarke describes the steroid as being either in solution or suspension, it is never in a different phase than the FFDH. Thus, where the steroid is described as being in solution, so is the FFDH. Clarke, claim 7. Likewise, where the steroid is described as being in suspension, so is the FFDH. Clarke, claim 8. Clarke neither describes nor suggests a formulation in which the FFDH is in suspension but the steroid is in solution, as claimed in the '302 application. And due to the technical difficulties associated with obtaining a stable FFDH suspension formulation having a steroid in solution, the claims of the instant application and those of the '302 application are not obvious variants of one another. *See* the second Declaration of Rudi Mueller-Walz which accompanies this response.

Applicant submits that the application is in condition for allowance and requests an action for same. Please charge any additional fees that may be due, or credit any overpayment, to Deposit Account No. 50-0311, Reference No. **28069-624N01,** Customer Number: **35437.**

Respectfully submitted,

/Muriel Liberto/

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